We have implied above that such a murmur might arise from the yielding of a valve after it had successfully withstood the pressure of the first part of the systole. We may conceive that disease of the papillary muscle supporting a segment of the mitral valve might so weaken it that it should be unable to stand the prolonged strain of the systole, although able to close the orifice by its contraction for an instant. Because of the brief duration of the maximum intraventricular pressure, however, this condition could not probably explain very late systolic murmurs, for if the valve did not yield during the time of highest pressure it would be unlikely to do so later. I do not, however, believe that this explanation applies to the case in hand.

Roy and Adami have shown that the final act in ventricular contraction is a pulling in of the auriculo-ventricular curtains by contraction of the papillary muscles. This causes a perceptible increase in the intra-ventricular pressure. If we may conceive that this pressure, in a given case, before their contraction, was so great that the action of the muscles, perhaps weakened by disease, was delayed an instant, and that, with the contraction, owing to dilatation of the ventricle and consequent spread of the base of support, the valve curtains were pulled apart, permitting regurgitation, we should have a beautiful theory of the origin of the late mitral systolic murmur.

I conclude, then, that in general we may explain these murmurs by asynchronous ventricular contraction. This theory is supported by the recognized frequency of such abnormal action of the heart in those cases in which the pressure in either system is abnormally increased. The right ventricle anticipates the contraction of the left in mitral disease, as we have seen, while the converse probably occurs in interstitial nephritis and other diseases raising the systemic tension above the normal. Confirming this hypothesis we have the recognition of basic reduplication in certain of the cases studied. I admit the plausibility in some circumstances of Griffith's explanation, and the possibility of the above-mentioned anomalous action of the papillary muscles in others.

CONCERNING THE ROLE OF INTRACELLULAR CATALYTIC PROCESSES IN THE PATHOGENESIS OF MALIGNANT NEOPLASMS.

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IT is now accepted as one of the truths of physiology, as well as pathology, that the cells of the mammalian organism may change their form, and even at times their structure, during their existence. Physiologically, they may change their forms under the influence of age, and according to many extrinsic and intrinsic influences to which they are subjected. It is often impossible to draw sharp lines of demarcation between that which is normal and that which is abnormal in such changes. Virchow expressed himself in the words that in reality there is no distinct line of demarcation between "physiological and pathological processes, and that the latter are only physiological processes which take place under difficult conditions." Cancer pathogenesis may accordingly be looked upon, in part at least, as a problem of growth of cells under difficult conditions, and in that case we have a right to expect that the solution of this problem may be aided by the adaptation and application of recent discoveries in physical chemistry to the pathology of cell growth, just as physical chemistry by its revelations concerning osmosis and the ionic theory has thrown light upon normal cell growth.

We have learned to look upon the individual cell as representing in itself a highly complicated system of organized parts, the latter standing in most intimate co-relation with each other. The cell may be conceived as representing on a small scale that which the entire cell state is on a grand scale, *i. e.*, a unity, a specific system of organized parts. Shall we seek the cause of malignant neoplasms, conditions of cell anarchy, caricatures of normal developmental processes, within or without the cell? This question separates all hypotheses concerning the etiology of malignant neoplasms into two great groups:

First, those assigning the cause of cancer to qualities inherent in the cells themselves. Secondly, those assigning the etiology of cancer to the action of some extraneous poison, particularly to the influence of micro-organisms. Although the latter theory may logically include the effect of toxins, even those not of bacterial origin, these two great groups may be concisely designated as, first, the histogenetic, and second, the parasitic theory, on the origin of cancer.

It is not my intention to discuss in this report the relative merits and demerits of these two groups of hypotheses. These matters are set forth in the various works on pathology, but most forcibly, perhaps, in the work of Professor David von Hansemann, *Die Mikroskopische Diagnose der Bosartigen Geschwülste.* Also in the work by Lubarsch, *Zur Lehre von den Geschwülsten,* in Ribbert's work, *Lehrbuch der allgemeinen Pathologie,* and in various editions of Lubarsch and Ostertag's *Ergebuisse d. Pathologie.* Hansemann, Ribbert, and Lubarsch are opposed to the parasitic theory, and by far the greater number of prominent German pathologists, while they are non-committal, have not given support to it. Recent American research work by R. B. Greenough, and Edward H. Nichols, published under the auspices of the Harvard University Cancer Commission, in the *Journal of Medical*

Research, 1902, vol. ii., invalidate the parasitic theory. On the other hand, the histogenetic theories, as examples of which we may mention those of Thiersch, "Der epithelial Krebs," Leipzig, 1865; Cohnheim, (*Allgemeine Pathologie*, Bd. i., S. 723) and Ribbert (l. c.) have the advantage that they cannot be controverted at all, being hypotheses pure and simple, without experimental foundation, so that they cannot be tested experimentally. The only excuse for the formulation of an hypothesis is that it gives the incentive to experimental investigation, and the formulation of inquiries into the nature of the thing discussed; and an hypothesis that does not permit of this has thrown no light on the subject to be solved, but simply side-tracked it. Thiersch conceived that the connective tissue might become weakened by disease or old age, and thereafter the epithelial tissues gain the supremacy and penetrate into the depths of other tissues. This theory does not explain the occurrence of cancer in young people, and cannot be tested experimentally.

Cohnheim conceived the cause of malignant neoplasms to be the supposed existence of congenital embryonal cells, which have remained latent in different tissues of the body. This theory does not explain why such undifferentiated embryonal cells, if they really occur, should suddenly begin to proliferate in an unrestricted manner.

This theory of Cohnheim has not become more probable by the discovery of unutilized segmentation cells of the frog by Roux,[1] who observed that in this animal, cells occurred which were not utilized, and were surrounded by growths of other cells. Barfurth observed the disruption and subsequent continued growth of a segmented portion of the exoderm. With regard to the mixed tumors it is very probable, however, that they can arise from disrupted embryonal germinal cells. Ribbert is of the opinion that this is particularly the case in sarcomas occurring in the very young.[2] Many of the tumors, particularly malignant tumors (glioma, teratoma, myosarcoma), would receive a satisfactory explanation of their histogenesis from the assumption that they grow from pre-existing dislodged embryonal cells. This is particularly true of tumors like carcinoma of the kidney developed from dislodged portions of the adrenal bodies. Ribbert assumes that these grow from portions of the adrenals which have been disrupted in an embryological state and continued to live in the substance of the kidneys. Such embryonal germinal cells may remain quiescent in the kidney parenchyma without forming a tumor, but under certain conditions which are not as yet thoroughly understood (Ribbert mentions hyperæmia), such cells undergo a rapid and progressive growth and multiplication. At first this is apparently a benign growth; it is well circumscribed and limited. But when it strikes a vessel and causes its wall to atrophy by pressure, it proliferates into the vascular lumen and may even cause metastases. The important point to bear in mind in the case of this tumor is that there are precursory stages which are not carcinomatous, and that they may persist in this benign state indefinitely. Evidently some additional tumor producing agency is necessary here to convert the benign growth from dislodgement of adrenal cells into the parenchyma of the kidney into a malignant growth. It shall be our duty in the following to approach a solution of this question, whether or not an additional tumor producing agency is necessary to impart the character of malignancy to cells already in a state of proliferation.

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[1] Anatomisches Heft, I. Abth., Heft 9.

[2] Loc. cit., p. 606.

Metaplasia. The transformations in form and structure which cells may undergo are important for the understanding of normal and pathological cell growth. Evidently if cells can change their specific structure and replace it by a different structure, which is, however, definitely differentiated or undifferentiated, it is not necessary to assume with Ribbert, that in all cases of mixed tumors we are dealing with disrupted or dislodged embryonal cells, as the starting point. Lubarsch's study of metaplasia suggests the possibility of the derivation of such tumors from metaplastic cells.

The *supposed participation of muscle, liver, cartilage and lymph gland cells* in the architecture of carcinoma metastases[1] are not genuine metaplasia—*i. e., transformation meaning the replacement of specific cell or tissue structure by other definitely differentiated structure of the same kind of tissue,* but they represent what Lubarsch cells pseudo-metaplasia, *i. e.*, the histological "cell accommodations" and "variations" of Hansemann—these are mere changes of form, not of structure. Naturally if the actual participation of the liver cells, etc., in carcinoma metastases derived from an original growth the stomach could be demonstrated, it would be a point gained for the advocates of the theory of infection for malignant neoplasms, but thus far their observations are cases of pseudo-metaplasia.

Lubarsch distinguishes three types of cell changes:

1. Pseudo-metaplasia—change in form but not of structure.

2. Metaplasia—structure transformation—replacement of specific cell or tissue structure by the different kinds of structure, but which is definitely differentiated and derived from the same type of tissue.

3. Undifferentiation—transformation of definitely differentiated cells into undifferentiated. Of this there are two types:

(*a*) Transient or physiological undifferentiation, occurring during progress of indirect cell division, during which typical structure is temporarily dissolved.

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[1] Rindfleisch, Klebs, Gussenbauer, von Leyden, XX. Verhandl. d. Congress f. i. Med.

(*b*) Pathological (permanent) undifferentiation which always leads to death of cells by degeneration or atrophy.[1]

Ribbert seeks the cause of carcinoma in an inflammatory proliferation, which disrupts the cell from its physiological connection. The cause of the unrestricted growth of the cell is the removal of resistance to growth in the environment caused by the inflammation. This theory does not explain why a carcinoma does not occur in every instance where an inflammation disrupts cells from their normal environment, and why carcinomas actually develop in the absence of every evidence of inflammation. It is seen that all of these theories have some resemblance. They all attribute the malignant neoplasm to some undefined power of growth within the cell and differ only in regard to the reasons assigned to this power of growth.

A fourth theory, which is that of Hansemann, does not concern the etiology of malignant neoplasms, but only their morphology and physiology. His conception is expressed in the word "anaplasia." Hansemann first used the word "anaplasia" in 1890,[2] from *ἀνα*, backward, and *πλάσσειν*, to build. He understands by it a condition in which cells have lost in part their specificity, have become "entdifferenzirt," so that they have acquired the property of independent existence, have lost what he calls "altruismus." He conceives that this anaplasia is brought about by abnormal, especially unsymmetrical, mitoses, and that some of the "idioplasm"[3] is thereby lost, while idioplasm which had previously been in the background now comes to the front.

Difficulties in the Way of the Parasitic Theory of Cancer. Above all we must recollect that the controlling histological elements in carcinomas are the connective tissue and the epithelial cells. These cells are the element which cause the tumor by their multiplication and advancement, and generate the metastases by their proliferation in other organs. We do not find such a phenomenon in the parasitic diseases. In all parasitic diseases it is the micro-organisms which transfer the diseases and then make a new inflammatory focus out of the elements and cells of the newly infected organ. In a parasitic disease the tissues of the newly infected organ itself compose the inflammatory tumor. In cancer the cells of the secondarily infected organ never participate in the metastasis; but this is composed exclusively of the cells of the organ primarily diseased. A primary cylindrical carcinoma of the stomach, when it causes a metastasis in the liver, never infects the cells of the liver, but the metastasis is composed of cylindrical stomach cells, or glandular epithelium from the mucosa of the stomach. This is true of other metastases. In no infectious disease do we find that cells from the primary focus of inflammation are driven about, nor do such cells of infectious diseases cause characteristic new-growths histologically like themselves in other organs.

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[1] Benecke's "Kataplasia"—Hansemann's "Anaplasia." For fuller account see O. Lubarsch, Arbeiten a. d. Anat. Abtheilung, d. kgl. Hyg. Instit., Posen, S. 209, 1901.

[2] Virchow's Archiv., Bd. cxiv., p. 321.

[3] Idioplasm. In biology, a term introduced by Nägeli for a special hereditary reproductive substance not contained in the body of the cell, but in the chromosomes of the nucleus, controlling and determining the actual characters of the particular cell, and also those of all its descendants. Each idioplasm is composed of several or many *ids*, which are capable of growth and multiplication by division; although much smaller in bulk than the rest of the living substance of the cell or body (trophoplasm), idioplasm is the active element in the process of formation, and determines the detailed construction of the trophoplasm, which is the passive element.

1. The parasites must live within the cell, and yet not injure it, in order to make the parasitic theory harmonize with the well-ascertained morphological facts concerning cancer proliferation. We must assume, then, a kind of symbiosis of parasite and cell. At the same time they must be able to bring into disorder the various finer cell parts already considered, in order that the incentive to cell proliferation shall be present. Whether such parasiticism is possible is doubtful.

2. As the unrestricted proliferation of the cells, as well as the power to form metastases, is ascribed to the presence of the parasites within the cells, it is necessary to assume that every cell contains a parasite, and that the parasite multiplies as rapidly as the cell, in order that each new cell shall receive its parasite. If the parasites do not divide in the identical moment that the cell divides, cells will eventually arise which contain no parasites, and, therefore, have no abnormal properties in the sense of the adherents of this theory. This condition necessitates that the cycle of development of the parasite should coincide with the rate of multiplication of the proliferating cells.

3. The best evidence points to the conclusion that transplantation of malignant neoplasms is successful only among animals of the same species. A parasitic disease, however, if we are permitted to draw inferences from the well-known infectious diseases, should be transferable from one species to another.

4. Primary carcinomas rarely occur in multiplies; only in exceptional cases of epithelioma of the skin has this been reported. Typical congenital malignant neoplasms (rhabdo-myosarcoma of the kidney, glioma of the retina) have been reported in children whose parents were not affected with malignant neoplasms.

5. The cells of organs invaded by cancerous metastases do not participate in the secondary growths. The metastases, with few exceptions, represent the cell type of the mother carcinoma.

6. Cells of a different type, then, being only exceptionally involved in the metastases, it is necessary to assume that every kind of cancer must have a special species of cancer parasite, which would not be capable of causing cells of another type to proliferate in a cancerous

manner. A pavement epithelial cell of the œsophagus, for instance, when it causes a metastasis in the stomach, produces a neoplasm composed of pavement epithelium; never cylindrical cell growth or an adenocarcinoma—structures which are found in the normal gastric mucosa.

ATTEMPTS AT EXPERIMENTAL PRODUCTION OF CARCINOMA. The special object of this report is to communicate in abstract a series of researches or efforts aiming at an experimental production of carcinoma of the stomach. This organ is more than all other organs in the body fitted for a study of cancer because it is more frequently invaded by this disease than any other organ or tissue in the body.[1] Not only this, but it is the only organ of which it is definitely known that a benign lesion, the peptic or gastric ulcer, may exist as such for months or even years and then can undergo changes transforming it into a typical malignant neoplasm. The scientific value of any series of investigations on cancer will depend very much upon the experience and familiarity of the investigation with the architecture and pathological physiology of these growths. It is for this reason chiefly that I confined my experimental studies to the adenocarcinoma of the stomach, believing that I could not be misled in confusing this characteristic growth with any of the other neoplasms of the stomach, or with simple inflammatory tumor. (See Hemmeter, *Diseases of the Stomach,* 3d edition, p. 527 to 586, on "Malignant Tumors of the Stomach.")

Gastric carcinoma may develop from the oxyntic or parietal cells (gland cells) of the peptic ducts, when they constitute the adenocarcinomas; but they may also arise from the cylindrical epithelium of the vestibules, and then they are termed cylindrical cell carcinomas; and finally, they may develop from the mucous glands; if the adenocarcinoma is restricted to the mucosa and grows outward, the stroma is composed of newly-formed connective tissue—if the carcinoma grows in the main muscular layer the stroma may be muscular tissue.

In 1898 I began with experiments attempting the transplantation of pieces of adenocarcinoma from the human stomach into the stomachs of dogs, cats, and guinea-pigs. I have a record of forty-two such attempts, but in not one case have I succeeded in successfully transplanting a piece of human concer of the stomach into the stomachs of any of these animals.[2]

In the *Journal of Medical Research,* vol. vi., No. 1, and vol. viii., No. 1, Dr. Leo Loeb describes the transplantation of tumors (sarcoma) through forty generations respectively of rats of different age and sex. In all cases a sarcoma was produced, and the details of the growth and generative changes of the cells were preserved. Even certain limits of variability in the cells were also preserved. Dr. Loeb assumes it to be a well-known fact that transplantation of cells[1] into animals of different species are usually unsuccessful, and this may account for the impossibility of producing a tumor in another species. The sarcoma which he found in the connective tissue of the parathyroid could never be successfully transplanted into any other species of animals. Guinea-pigs, animals so susceptible to tuberculosis of different origin, remained absolutely unaffected by these tumors. He suggests that certainly none of the ordinary micro-organisms can be the cause of these new-growths, of which there was no doubt that they were true sarcomata.[2]

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[1] The literature and statistics on this subject will be found compiled in a volume by Behla, "Die Carcinomlitteratur" (up to 1900), pages 244 and 248.

[2] The literature on transplantation of cancer from man to animals is compiled in "Ueber die Actiologie des Carcinoms," by Gustav Fütterer, Wiesbaden, 1901. It appears from this compilation that 11 experimenters claimed to have had successful transplantations, but 19 others had negative results. A number of other transplantations are mentioned and criticised in Hansemann's work, loc. cit., p. 174.

In a more recent contribution, Mayet[3] reports transplantation experiments, in which he introduced pieces of human cancer into animals subcutaneously, or by rubbing up pieces of human carcinoma with sterile bouillon, and injected the resulting emulsion into the peritoneal cavity, or into the circulation of animals. Most frequently, however, he injected a glycerin extract of human cancer tissue, aseptically mascerated, or a filtrate obtained by filtering such crushed tissue through a Pasteur filter or an asbestos filter. Previously, the animals used received cantharidin injections, with which he aimed to produce transitory nephritis and so to predispose the kidneys to the development of cancer nodules. Mayet experimented on dogs, rabbits, and white rats. He admits that his experiments on dogs and rabbits were unsuccessful, but claims that he succeeded in certainly producing cancer lesions in three white rats out of fifty-three of these animals experimented upon. These alleged successful cases he claimed were produced by the glycerin extracts or filtrates from human carcinoma. A critical study of Mayet's paper leads one to be especially skeptical concerning his claim of having produced a genuine carcinoma in this manner. He does not describe the typical architecture of a carcinoma, but speaks of epithelial cancerous lesions.

An interesting series of experiments on tumor transplantations and inoculation is described by Dr. M. Herzog.[4] The original animal which Herzog used was a descendant of the white rat from which L. Loeb[5] derived his sarcoma. The growth was a vascular cystic sarcoma of the thyroid in a rat. Over fifty successful transplantations were made in the same species of animal, and these extended over eight tumor generations. In the inoculation experiment of Herzog, pieces of non-infected sarcoma were ground up in a sterile mortar with sterile quartz sand and silicon powder. The tissues were ground up with physiological salt solution—the emulsion so prepared filtered through a Pasteur filter, and the filtrate so prepared inoculated into culture tubes, showing it to be free from microorganisms. Several cubic centimetres of this filtrate were injected into the abdominal cavity of rats—not a single one of the rats so treated developed a tumor. Some were killed and examined, and the findings were absolutely negative. Thus far Herzog's investigations are clear and instructive; but further on he mentions the possibility of ultramicroscopic organisms, too small to be seen even by the aid of our best optical instruments. He claims that bovine pest can be propagated by filtrate through a Pasteur filter, and that the work of Nicolle and Abdil Beyer gives evidence that the cause of this disease must be a living organism which can pass through a Pasteur filter. I am not sure that the work of Nicolie and Abdil Beyer justifies such a conclusion.[1]

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[1] The literature on the transplantation of cancer cells from animals to animals is compiled in the work of Fütterer, Bebia, Hansemann.

[2] Loc. cit., p. 49.

[3] "Production du Cancer chez les Rats blancs Introduction dans leurs Economies des Substances constituantes des Tumeures malignes de l'Homme?" Gaz. hebdom. de Medic. et de Chir., January 19, 1902, No. 6, p. 64.

[4] Journal of Medical Research, vol. viii., No. 1, p. 74.

[5] Loc. cit.

I have given these previous experiments such detail because they express in the work and words of others much of the work and experiment which I have made personally, yet never published. I have also prepared a sterile filtrate of human carcinoma of the stomach, exactly in the manner as described by Herzog, and injected it into the stomach tissue of dogs, cats, and rabbits, but never succeeded in causing a gastric malignant neoplasm in these animals by this process.

It is a well-known fact of pathology that the human gastric or peptic ulcer may become transformed into an adenocarcinoma, apparently spontaneously. This process has been described in a classical investigation by Hauser.[2]

In 1900 I paid a visit to Professor Hauser's laboratory at the University of Erlangen, and was fortunate enough to see some of his original preparations and sections. I have also had a rather exceptional clinical experience with cases of gastric ulcer in the human being, which I had studied, in one case, for over two years, during which it presented the typical clinical history of gastric ulcer. Then followed the clinical history of gastric carcinoma and death.[3] Naturally, the question arose in my mind, "*If gastric ulcers could be produced experimentally in animals, their transition into possible adenocarcinoma might be studied at*

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[1] As far as I know the experiments of L. Loeb and M. Herzog have not been confirmed by others, nor am I in a position to judge whether the neoplasms they claim to have produced were genuine sarcomas.

[2] Das chronische Magengeschwür, sein Verharbungs-Process und die Beziehung zur Entwickelung des Magencarcinoms," Leipzig, 1883; and "Das Cylinderepithelcarcinom des Magens und des Dickdarms, Jena, 1890. See, also, New York Medical Record, 1897, vol. lii. p. 365; also, Hemmeter, "Diseases of the Stomach," third edition, p. 560.

[3] See Hemmeter, New York Medical Record, 1897.

will, or the transformation into adenocarcinoma might be attempted by the transplantation of malignant neoplasms derived from other animals of the same species, or by the injection of sterilized filtrate of ground-up adenocarcinoma of other animals of the same species into the tissues surrounding the edge of the ulcer."

Among the causes that are definitely ascertained as contributing to the bringing about of gastric ulcer are especially three:[1] first, impaired vitality or injury to the mucosa of the stomach; second, hyperacidity or supersecretion of gastric juice containing an excess of HCl, and proteolytic ferments; third, an altered or impaired state of the blood.

All three of these factors may be produced artificially, and when we do produce them in the laboratory on animals, peptic ulcers arise in such a large proportion of the animals thus experimented upon, that we have a right to conclude that they are directly attributable to the method pursued. When I speak of peptic gastric ulcer I mean the typical "chronische magengeschwür" as described by Hauser. For defects can be produced in the dog's stomach, for instance (and the literature on the experimental production of gastric ulcer proves this conclusively), which are not true gastric ulcers, but simply ulcerating lesions, which heal rapidly. Gustav Fütterer has produced such lesions by applying to the stomach caustics, ligating the gastric arteries, cutting off the supply of nutrition by stitching large portions of the mucosa with catgut sutures. Defects resulted, but they all healed in a short time. Even when one-third of the quantity of the animal's blood was withdrawn such defects had healed in two weeks. In 1896 Silbermann[2] produced gastric ulcers in dogs by either tying the gastric arteries or causing emboli in them by injecting suspensions of lead chromate. Thereafter he injected hæmoglobin and pyrogallic acid. When Fütterer resected the gastric mucosa, as stated before, and made injections of pyrogallic acid, he could confirm Silbermann's results, and produced ulcers of the stomach which in every histological detail corresponded to the chronic gastric ulcer of the human being. By making use of this method employed by Fütterer and Silbermann I was successful in producing experimentally gastric ulcers in one series of experiments; eleven dogs out of thirty operated upon developed typical gastric ulcer.

Now I had a method by which this characteristic lesion could be produced experimentally. The next question was, "Could these lesions be in any way experimentally transformed into adenocarcinoma of the stomach, or could they become transformed into adenocarcinoma spontaneously, as has been definitely known to occur in the human being, and as Fütterer has observed, to occur in a rabbit, in which he had artificially produced a gastric ulcer by the method described?"[1]

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[1] See Hemmeter's "Diseases of the Stomach," third edition, p. 491.

[2] Experimentelles in klinisches zur Lehre von Ulcera Ventriculi rotundum. Deutsch. med. Wochenschr., 1886, No. 29, p. 497.

Hauser has described a structural characteristic of the adenocarcinoma of the stomach, which had developed on the basis of a gastric ulcer, and which is not observed in ulcerating carcinomas not developed on this basis. This characteristic by which the so-called "ulcus-carcinomatosum" can be recognized, consists in a very peculiar behavior in the fibres of the chief muscular layers of the stomach, and also of the fibres of the muscularis mucosæ. This peculiar behavior of the muscularis consists in an oblique ascension of the fibres of the true muscular layer, and a descension of the fibres of the muscularis mucosa, the fibres of both muscular layers converging toward and fusing into each other in front of the edge of the ulcer, which is here composed mainly of connective tissue. The true muscularis bends upward in continuity, and the border of the ulcer, which is composed of very dense connective tissue, is limited by the lower or peritoneal strata of the turned-up true muscularis.

Another feature of the ulcus carcinomatosum is that a section made perpendicularly to the surface of the stomach, and through the entire bed of the ulcer, almost invariably exhibits the general outline of a fish-hook.[2] For the causes which bring about this fish-hook formation,[3] the main reason being that the lower edges of the ulcer near the pylorus are, during the efforts of gastric peristalsis to evacuate the chyme into the duodenum, exposed to the most mechanical irritation, and, accordingly, Fütterer has shown that adenocarcinoma, if it develops from an ulcer, always develops from the lower edge. This location for the development of gastric ulcer had already been emphasized in a publication by Dr. Delano Ames and myself, but it is the merit of Fütterer to have emphasized this point as an etiological factor in the causation of ulcus carcinomatosum.

I should add that in repeating the experimental production of gastric ulcer, according to the methods of Silbermann and Fütterer,[4] I not only produced mechanical defects, and injected pyrogallic acid in the method described, but I maintained a very high acidity for free HCl in the gastric chyme of the dog by supplying this acid in his food and also pouring it into his stomach through a soft rubber tube. In February, 1900, I came into the possession of a mongrel fox-terrier, who persistently vomited his food. The vomit contained no free HCl or ferments, and at the autopsy a cancer of the stomach was found near the pylorus. Transplantations with this material were made into the stomachs of other fox-terriers, but I was not successful in producing a gastric carcinoma in any other animals inoculated.[1]

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[1] Loc. cit., p. 152.

[2] See Hemmeter, "Diseases of the Stomach," third edition, plate ix., opposite p. 506; also New York Medical Record, loc. cit.

[3] Loc. cit., p. 112.

[4] New York Medical Record, September 11, 1897.

In the meanwhile the publication of Fütterer appeared, and it occurred to me that possibly my failure to successfully transplant canine carcinoma was due to the fact that the stomach of the animal into which the inoculation was made was not in a susceptible condition, and that it must be transformed into such a condition by a previous injury. This previous detriment to the tissue, in order to secure successful transplantation of the tumor, has in the case of rats not been found necessary by Leo Loeb and M. Herzog. I did not succeed in securing another dog affected with carcinoma of the stomach until after I had read Fütterer's work in 1901, and this second dog presented an adenocarcinoma which developed spontaneously at the edges of an experimental gastric ulcer. It presented the behavior of the two layers of the gastric muscularis, as first described by Hauser, had a distinct fish-hook form, and exhibited heterotopia of gastric glands, as first described by Virchow[2] and Hansemann.[3] This gastric cancer reached the size of a walnut, and two metastases were found in the omentum. It was this carcinoma which was used in making a filtrate with which the edges of the peptic ulcer previously produced in other dogs were injected.

It will be seen that these experiments are attended with unusual difficulties in procuring the material, for if we wish to study the effect of extract of adenocarcinoma upon experimentally produced gastric ulcer, we must have two sets of animals: one presenting the cause and the other the gastric ulcer. If we should accidentally come across a dog with an adenocarcinoma it would take at least two or three weeks to get a number of other dogs having experimental gastric ulcers. It is a matter of great difficulty to determine in the live animal whether it is really afflicted with gastric cancer, and if the cancer is accidentally found at autopsy in a veterinary school, it rapidly decomposes, and unless kept on ice the canine gastric cancer becomes useless for experiments in two or three days, for bacteria, especially the pus cocci, are great hinderances to successful transplantation, as Loeb[4] has emphasized. We will, therefore, in future, have to depend on cancer tissue gotten from living dogs, or soon after the autopsy, or such cancer tissue produced experimentally by the method of Fütterer, which in my experience only succeeds in one-third of the animals experimented upon.

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[1] Sepsis followed a large proportion of the operations, and I could not secure the aid of a competent surgeon who would do these operations aseptically for me. A sterile extract of part of this canine carcinoma was also made and prepared for inoculation and injections into dogs, in which I expected to cause gastric ulcers. A very small quantity of filtrate (48 c.c.) was thus saved, as the largest part of the tumor had been used for transplantations.

[2] Virchow's Archiv., Bd. 111.

[3] Loc. cit., p. 195.

[4] Loc. cit.

The adenocarcinoma which developed at the edges of the experimental peptic ulcer was found at a time when I was engaged in producing such ulcers in a series of animals. Eight transplantations of such tumor particles were made into the edges of peptic ulcers of other fox-terriers. Five of these animals died of infection and other intercurrent accidental complications. Three of them lived each three months after the transplantation, and of these three, two had developed adenomatous proliferations closely resembling carcinoma at the edges of the gastric ulcer nearest the pylorus.

SUMMARY. Eight dogs afflicted with experimental peptic ulcer, inoculated by injecting tumor particles made of suspension of the tumor cells of a gastric adenocarcinoma into the edges of the gastric ulcer. Five of these animals died of sepsis, etc., three of them lived three months each; developed symptoms of gastric carcinoma, and in two of them the adenomatous proliferations described by Hauser and Fütterer were evident at the pyloric edge.

This method of inoculation by a suspension of the tumor cells was preferred to transferring actual pieces, because I had a very small original tumor to start with, and for the purpose of demonstrating the principle involved, it makes no difference whether we transfer large pieces or only a few cells, for any ensuing development of carcinoma can only in these cases be attributed to a further growth of the injected carcinoma cells, or whatever hypothetic micro organism or tumor producing agency they may be assumed to carry. My main object, however, was to discover whether the cancer formation at the edges of gastric ulcers could be induced by the injection of a fluid gained from canine carcinoma and free from carcinoma cells as well as micro-organisms, as far as our modern methods of testing these two points permit us to judge.

PRODUCTION OF EFFORTS AT ADENOMATOUS PROLIFERATION FROM THE EDGES OF PRE-EXISTING EXPERIMENTAL GASTRIC ULCER BY THE INJECTION OF CELL-FREE AND STERILE EXTRACT OF CANINE GASTRIC ADENOCARCINOMA. The sterile and cell-free extract of canine gastric adenocarcinoma was prepared by grinding up non-infected portions of this cancer in a sterile mortar with quartz sand, together with physiological salt solution. Then this emulsion was filtered through a Pasteur filter, and cultures made upon a number of the most commonly used media, which proved negative. In order to exclude the possible action of bacteria, I might of course have used strong antiseptics in the solution, such as bichloride of mercury, formaldehyde, carbolic acid, etc. There are, however, two grave objections to this way of proceeding. I shall have to premise what I intend to say by stating that I had from previous observations and experiments gained the impression that the tumor producing agency in these cases was not the cell itself, nor a micro-organism, but an enzyme, which had passed through the filter. The first objection to using antiseptics or heat in sterilizing the filtrate was that whilst they no doubt could destroy any micro-organisms, a sufficient degree of heat, as well as the more effective antiseptics, would also destroy any possible enzyme present. The second objection to using these substances was that any possible effect upon transforming the peptic ulcer might have been ascribed to the antiseptic use or to chemical additions to the filtrate and not to any inherent qualities derived from the original tumor. I have, however, shown that thymol, even in saturated solution, has no such destructive action upon the proteolytic ferments of the intestinal canal.[1]

A. S. Loevenhart and Kastle, in their beautiful investigation on the reversibility of the action of lipase[2] and Loevenhart in his researches on lipogenesis[3] toluene was used to keep the tissue extracts sterile, and evidently the effectiveness of lipase was not impaired by this antiseptic. In one of my successful experiments I also made use of toluene, and I believe this excluded the possible action of any bacteria that might be presumed to pass through a Pasteur filter. From the investigations of William G. Wherry[4] concerning the permeability of the Berkefeld and the Pasteur-Chamberland filters to bacteria of small size it seems justifiable to conclude that bacteria of small size can pass through them. The bacillus producing pneumonia in guinea-pigs, for instance, will pass through the pores of a small Berkefeld filter, No. 5, and sometimes organisms which do not pass through the above filters, like the bacillus coli communis, may grow through. Referring once more to the work of Herzog, it seems justifiable to conclude from the results of Wherry, that if the virus of a disease passes through the pores of a Berkefeld filter, it is not necessarily ultramicroscopic. The practical import for our research was that we could not rely exclusively upon filtration, but had to resort to some antiseptic in order to attain an absolutely sterile liquid. For this purpose thymol, and in some cases toluene, were used.

As far as the methods at present at our disposal permit me to judge, the filtrate extract used for these inoculations was sterile. The injection of filtrate into ten animals afflicted with experimental gastric ulcer resulted in four of them in the development of adenomatous proliferation closely resembling an adenocarcinoma at the edges of the ulcer. The time in which the animals were examined after the first injection varied

[1] Hemmeter, "Ce que Deviennent les Ferments Digestifs—Bacteries proteolytique du Colon," XIII. Congres International de Médecine, Paris, 1900, also "Ueber das Vorkommen von Proteolytischen und Amylolytischen Fermenten in Inhalt des Menschlichen Kolens," Pflüger's Archiv. f. die ges. Physiologie, Bd. 81, 1900.

[2] American Chemical Journal, xxiv., 1900.

[3] American Journal Physiol., vol. vi. p. 331.

[4] Journal of Medical Research, November, 1902.

from twelve to fifteen weeks after the first injection. The histological characteristic of the carcinomas developed corresponded closely to those described by Hauser and Fütterer: (1) There was a diffuse proliferation of glands; (2) heterotopia of gland cells; (3) the cells of the proliferated gland ducts stained apparently as deeply as the normal cells in the same section; (4) there were numerous mitoses in the proliferated gland cells, some of them atypic, and also mitoses in the connective tissue cells close to the proliferated glands. Notwithstanding these histological characteristics, I am by no means of the opinion that the proliferation produced in this way was really a malignant neoplasm, for I have observed such proliferations around two peptic ulcers that were excised by operation, and the patients remained well eight and nine years respectively.

The question arises if the adenoma thus produced was not caused by the implantation of a carcinoma cell, nor by infection with bacteria, what did cause it? This question opens a wide field for reflection. If the Pasteur filter can keep bacteria as well as cells from passing through, the incentive to growth can only have been given by some chemical substance capable of passing through the filter, and contained in the filtrate. This substance was extracted from a pre-existing carcinoma in a dog. But it is essential to bear in mind that in one case the gastric ulcer developed into a carcinoma spontaneously. Evidently the cellular tissue of the stomach, in its abnormal condition, is capable of producing in itself the tumor forming agency, and whatever a tissue can produce out of its own cellular structure, if it can be proven that the tumor producing agency is not a bacterium, must be a product of the cells themselves, and very probably inherent in the cells.

COMPARISONS OF THE RELATIVE OSMOTIC PRESSURES OF NORMAL CELLS AND CARCINOMA CELLS OF THE SAME ORGAN. Normal cells, as well as carcinoma cells, can be isolated from their stroma by pencilling portions of fresh tissue in salt solution, isotonic with the blood plasma. The strength of this solution will vary with different animals. The serum of human beings is, according to H. J. Hamburger,[1] isotonic with a 0.84 to 0.89 per cent. solution of sodium chloride. I have observed cells from a carcinoma of the stomach in such salt solution on the warm stage, and compared them with the cells of normal stomach tissue. Whilst there was no apparent change in the normal gastric cells the gastric carcinoma began to contract in the course of the day, four to five hours, as if they were in an hyperisotonic solution. Not all cells of gastric carcinoma that are pencilled out in an isotonic salt solution will show this contraction. One notices that in perhaps one-fourth to one-third of the cells there is no contraction evident. I have gained the impression that although carcinoma cells represent cells that are emancipated from the laws of normal proliferation (if I may speak of such laws), nevertheless the carcinoma cells themselves, although alienated from the general cell state, may be healthy or diseased. By healthy in this sense I do not mean that they are normal cells; but simply that they represent a condition of the cells as occurs in the majority of cancers before they begin to disintegrate. When a cancerous tumor undergoes necrobiosis certain of its cells undergo a still further pathological process and it is in these cancers undergoing cellular destruction in which the perfect lawlessness of the cancer cell becomes manifest. I am of the opinion that those cancer cells which do not act like the majority in isotonic salt solution are perhaps already undergoing the beginning changes of necrobiosis. The majority of cancer cells show a contraction, whereas this minority does not show this phenomenon. Difference in staining of the protoplasm and chromosomes can also be observed in these two kinds of cancer cells. I am in doubt whether this phenomenon of contraction or swelling, as the case may be, would be possible in the cells of all types of cancer. The adenocarcinoma of the stomach is derived from an epithelial and glandular cell which even normally gives evidence of marked regenerative power. It possesses marked mutability, as Virchow would say, and these powers are still manifest when this cell becomes emancipated from the normal laws of proliferation. I have not been able to try the experiment, but I doubt whether the cells of an osteoma, chondroma, or scirrhus would be capable of undergoing visible osmotic changes under the microscope, no matter how different the osmotic tension of their environments would be made from the tension existing within their protoplasm.

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[1] Osmotischer Druck und Ionenlehre, p. 445.

Similar observations were made with the cells of a mammary carcinoma, comparing their behavior to that observed on normal mammary gland cells in isotonic solution. I have also compared the behavior or normal gastric gland cells with those of a gastric adenocarcinoma after they had been pencilled out in the blood plasma of the same patient, and also in the blood plasma of another but normal individual. The same differences were found between the two in blood plasma as observed in isotonic salt solution. These studies led me to suspect that a deep-seated disturbance exists between the osmotic tension of the living cells of a cancer and the surrounding juices, mainly because the cancer cells act differently from the normal cells of the same tissue when placed in the same isotonic solution or in blood plasma of the same individual. Thus far these studies have been made only in mammary and gastric adenocarcinoma, and I would caution against the extension of the observations to all forms of tumors until these have been thoroughly studied in this way. It must be emphasized here that as these pieces of tissue could only be gained at operation, I was restricted in my search for normal cells to tissue in the immediate neighborhood of the malignant growth. It is probable that cells of the same organ, more remote from the malignant growth, might have shown a still greater contrast. I am now studying the behavior of normal cells observed in cancer juice expressed from a cancer of the same organ. Normal cells of an organ observed in such cancer juice will give evidence of swelling in the course of three to five hours. These phenomena might be interpreted by differences in osmotic tension between the protoplasm of the cell and the surrounding solution. For instance, if a normal cell swells up in filtered cancer juice, we may be correct in assuming that it takes up water, that the cancer juice contains relatively more water than the protoplasm of the cell. Increase of volume of the cell, if associated with cytolysis, may be due, however, to the presence of toxic substance in the cancer juice. This has at present not yet been satisfactorily investigated. The fact that the majority of healthy cancer cells contract in salt solution isotonic with blood plasma would indicate that they have lost water. It is justifiable to assume that the osmotic tension between a cancer cell and the normal cancer juice as existing in its environment is isotonic, for a cancer cell will not change its volume in cancer juice. However, in the production of this juice it is unavoidable that the cancer cells are cut and bruised and considerable of the cytoplasm of the cancer cell may be contained in it, which is not present in the juice bathing the cancer cells in the ordinary state of these growths. Material is very difficult to obtain, for although the cancer tissue is readily obtained from operators, they do not, as a rule, cut far away from the limit of the growth into the normal tissue in an effort to remove it.

These are purely physical conditions, but they show a definite disturbance of osmotic tension.

Phenomena of cell division are as Bütschli, Quincke, and Jacques Loeb believe, phenomena of protoplasmic streaming. They require, as Quincke has shown, a definite degree of viscosity. We have to remember that all life phenomena, normal as well as abnormal, are ultimately due to motion, or changes occurring in colloidal matter.[1] No protoplasmic motion can occur if the normal viscosity of this matter is disturbed in either direction, that is, if it is too great or too small. It may be that the disturbances in osmotic pressure, which I have suggested in the preceding, may lead to changes in the viscosity of cell protoplasm, either favoring or inhibiting cell division.

CHANGES IN VOLUME WHICH NORMAL CELLS UNDERGO IN CANCER JUICE. Studies on osmotic pressure made by means of the hematokrit, according to the methods of Hedin[1] and Köppe,[2] indicate that normal cells of the stomach or mammary gland cells when placed in cancer juice derived from a gastric or mammary cancer, swell up as if they were in a hypisotonic solution. The red blood cells of normal human beings and also of cancer patients will lose some of their coloring matter when placed in sterile cancer juice or sterile filtrate made as described in the preceding portion of this article. This would, in some of my studies, occur even when this filtrate or cancer juice was made isotonic with the blood plasma, and is suggestive of a substance in the cancer juice which is capable of making the stroma of the blood corpuscles permeable to toxic or other substances capable of effecting dissolution of the hæmaglobin; and reminds one of the experiments of Belfante and Carbon,[3] and also those of J. Bordet.[4] These experiments demonstrated that toxic substances are formed in the blood serum of animals into whom blood of another animal species had been injected. If the blood of a rabbit is injected into the peritoneal cavity of a guinea-pig, the serum of the guinea-pig blood will acquire the property of destroying the red blood corpuscles of rabbits, a property which the serum of normal guinea-pigs does not possess. If 5 c.c. of serum of a normal guinea-pig are injected into the circulation of a rabbit, this animal is in no way influenced thereby. But if this serum is derived from a guinea-pig which has previously received several injections of rabbit blood, then it becomes dangerous to a rabbit. A few minutes after the injection the rabbit dies and the autopsy reveals extensive dissolution of the blood and numerous hemorrhages as a consequence. Similarly the blood of the guinea-pig can be made to acquire a destructive property upon cholera bacteria after a small amount of a culture of cholera vibrios have been injected into the peritoneal cavity of the guinea-pig. Ehrlich and Morgenroth[5] and the other authors agree that this hæmolytic and bacteriolytic action of guinea-pig serum is due to two substances, one of which they speak of as a "sensibilisator," and the other as an "alexin." It is the penetration of the "alexin" into the red blood corpuscles which makes it lose its coloring matter, but this "alexin" cannot work unless the blood corpuscles have been sensibilized by the other agent. The "sensibilisator" is formed in the circulation of the guinea-pig by the intraperitoneal injection of rabbit blood. The "alexins" are normally present in the circulation of the animal. It was discovered that the sensibilizing substance can tolerate a temperature of 70° C. without destruction, but that the "alexin" is destroyed at a temperature of only 55°. I have said that the normal serum of the guinea-pig contains "alexins," which are preserved, of course, in the serum made active against the blood corpuscles of the rabbit. If the active guinea-pig serum is heated to 55° the "alexin" is destroyed, but the sensibilizing substance remains active. In such a serum the rabbit blood corpuscles retain their coloring matter, for the "sensibilisator" is not capable of producing hæmolysis. But as soon as serum from a normal guinea-pig or a normal rabbit is added, the coloring matter of the blood corpuscles begins to part from the red blood cells, for both the normal guinea-pig as well as rabbit serum contain "alexin." These agents which produce hæmolysis partake of the nature of catalytic agents. Ehrlich and Morgenroth speak of "*Zwischenkörper*" (intermediate bodies), and also of "*complement.*" In none of these investigations is it stated that these substances have been isolated.[1] The speculations concerning them are based exclusively upon an observation of their effects. They were important for me, however, in suggesting the idea that perhaps the cell growth representing cancer might in some way be associated with the influence of a catalytic agent which could be studied in a similar manner by its effects on the normal cells of the same tissue or upon the blood cells of the same or normal individuals. The effects which I have observed of cancer juice on normal cells of the same organ, and of cancer juice and cancer filtrate upon blood corpuscles, throw no direct light upon the pathogenesis of malignant growths. They were undertaken merely because such studies had, to my knowledge, not been undertaken heretofore, and I felt that I was following the injunctions of Julius Robert Mayer that a phenomenon should be studied from every possible aspect before we should seek consolation in an hypothesis. Then again there was the hope that some reaction might be discovered whereby we might be enabled to tell what was a malignant growth and what was not, by the effects of the juices of a malignant growth upon normal cells. This has, so far as my work is concerned, not as yet been successful. The question is so manifold and the liability to error in whatever direction one goes is so great, that no practical conclusions should as yet be drawn. A weak point of these investigations consists in the fact that the juices and filtrate extracts of benign growths have not as yet been studied in their possible action upon cells of the same organ, or upon blood cells, nor even have the tissues and filtrate extract of normal tissues in their actions upon each other been studied satisfactorily. The question might be asked, "Does the tissue of an entirely normal stomach contain an agent concerned in the cell growth of gastric tissue which on being extracted from a whole stomach, concentrated by aseptic evaporation, and injected into normal gastric tissue of another animal of the same species, will cause increased growth of that tissue?" For the development of the growth of the mucosa we would have to limit ourselves entirely to extracts of the mucous membrane, for the stomach contains layers of widely different cellular structure. If such an extract of mucosa does not affect the normal stomach would it cause cell proliferation after being injected into the edges of a gastric ulcer? As the difficulties of this investigation seem almost insurmountable, depending largely on procuring proper and abundant material, I have given expression to these suggestions with the hope that they may be of value to other investigators.

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[1] Jacques Loeb, "The Comparative Physiology of the Brain, etc., p. 14.

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[1] Skandinavisches Archiv. f. Physiologie, 2, 134, u. 360.

[2] Dubois-Raymond's Archiv., Physiol. Abt., 1894, 154.

[3] Referred to by Metschnikoff, Annals of the Institut Pasteur, June, 1900, No. 6, p. 370.

[4] Ibid., October, 1898, April, 1899.

[5] Berliner klin. Wochenschr, 1899, Nos. 1 and 22.

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[1] I shall apply the inspiration gained from the work of Bordet, Ehrlich, etc., in the explanation of the rarity of metastases, under the heading of "Metastases," later on.

This much I will have to emphasize, "Whatever the substance or agent may be which causes a benign canine gastric ulcer to be transformed into an adenoma," it is destroyed when the filtrate is heated to 60° C. (140° F.); for while four animals out of ten injected with the unheated filtrate developed adenoma, no such result followed in six animals afflicted with gastric ulcers when they were injected with the filtrate that had been heated to 60° C.[1]

PROBLEMS OF CELL GROWTH. All of these questions are intimately related with the *problems of cell growth.* The immediate and specific causes of cell division are still imperfectly known. Is cell proliferation due, as Ribbert[2] thinks, exclusively to the removal of inhibition or restrictions to growth in the environment of the cell, or is it due to proliferative forces within the cell? We have thus two conceptions of the immediate causes of cell growth, one without and the other within the cell. According to Thiersch and Boll, each tissue continues to grow up to the limit afforded by the resistance of neighboring tissues or organs. In the fully developed body the mutual relations of the cells are of such a nature that the conditions for further proliferation are unfavorable. Ribbert and others express this in the term "tissue tension" ("*Gewebe spannung*"), which prevents an increase of growth in the cells. They understand by this "tissue tension" all the mutual influences of the tissue constituents upon each other; they do not exactly mean mechanical pressure, although this no doubt plays an important rôle in restricting growth. The removal or lessening of this resistance to growth through injury or disease causes the resumption of growth and cell division, leading either to regeneration of lost parts or the formation of abnormal growth. According to the precedent of Virchow, it was formerly held that not only the function of a cell, but also its growth could be directly caused by the action of external stimuli. Virchow distinguished, accordingly, between functional, nutritive, and formative stimulation. This doctrine was contested by Weigert, whose efforts to disprove the power of external agencies to stimulate directly cells to proliferation have been very instructive. Weigert postulates that some primary injury to the tissues, as the immediate effect of chemical, mechanical, and other external agencies, is necessary to stimulate growth. This postulate has been fulfilled in many instances where such a cell injury had not been previously suspected. Better methods of investigation will no doubt enable us to demonstrate such an injury to the tissues. At the same time it is going too far, in my opinion, to attribute all morbid cell growth to such cell injury. In a comprehensive way Weigert's theory may be stated as follows: Cells are incited to growth through removal of obstacles to growth in the environment, in consequence of some disturbance in the normal relations or equilibrium of the cells with surrounding parts. The capacity of cells to proliferate has become latent when a certain "tissue tension" has been reached; it has become potential by the establishment of definite relations between cells themselves and between the cells and the basement substances, bloodvessels, lymphatics, tissue juices, and chemical substances contained in them.

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[1] I am refraining from designating the proliferation as carcinoma for reasons given at end of article.

[2] Loc. cit., p. 300.

We have hitherto studied cell growth as conceived to be due to a removal of restriction to proliferation outside of the cell body. In all these cases, however, it is difficult to determine the immediate stimulus to cell division, for a long chain of causes and effects may intervene between the primary disturbance and the ultimate reaction of the dividing cells. The opinion is gaining ground that the immediate causes of cell proliferation, whatever their antecedents, are to be sought in local chemical changes. Recent experiments on the proliferation in the ova of various invertebrates, conducted by Jacques Loeb, T. H. Morgan, R. Hertwig, and Mead, give ground for the conclusion that the stimulus to cell growth is of a chemical nature.[1] The climax of these experiments is reached in Loeb's artificial production of parthenogenesis in sea-urchin eggs by treatment with dilute magnesium chloride. The remarkable gall formation in plants leaves no doubt that extremely complex abnormal growths may result from specific chemical stimuli, and pathologists have held that abnormal growth in the animal body may also be incited by abnormal local chemical conditions. Only in two ways, then, can the cell be incited to growth—either by the removal of resistance to growth in the environment or by an increase in the formative energy resident within the cell. William H. Welch[2] concedes both of these possibilities—*i. e.*, forms of energy acting from without directly increasing the formative energy of the cell, and stimulating it to growth and multiplication; and, secondly, increase of the proliferative forces naturally latent (dormant) within the cell. It will be difficult to decide in which of the two ways cell proliferation is brought about. One reason for assuming that in carcinoma of the stomach the tumor producing agency is to be sought in increase of the proliferative forces within the cell is the fact that these cells must be ground up and crushed very thoroughly before the extract will have any cancer converting effect upon experimental gastric ulcer. If the tumor producing agency were some chemical substance in the environment of the cell, we should not expect that thorough crushing and grinding were necessary to extract it, but that it could be dissolved out by repeated percolation and irrigation. However, this is an unreliable test, as the tissues must be torn up into small pieces in both instances, even if only to permit percolation. The fact that it is possible to extract a tumor producing agency from gastric carcinoma by crushing pieces of it in normal salt solution would not permit us to decide whether the tumor producing substance was derived from within or without the cell.

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[1] Edmond B. Wilson, "The Cell in Development and Inheritance," second edition, p. 391.

[2] Adaptation in Pathological Processes, THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, June, 1897.

The modern view that cancer metastases can be effected by the transportation of single carcinoma cells is a support of the contention that the tumor producing agency is resident within the structure of the cell. In a recent investigation on the fate of dislodged and embolized tissue particles in the animal body, Paul Lengermann comes to the conclusion that the power of producing metastases is dependent upon an increase in the proliferative energies inherent in the cell, and not upon a reduction of normal tissue resistance to growth.[1]

Speaking of the influence of cell nutrition and the maintenance and undisturbed progress of cell function, Ludolf Krehl[2] says: "Nobody will expect that a tissue can maintain form and size without sufficient supply of potential energy; but the incentive does not come from the blood, as was formerly believed, but always from the parenchyma itself."[3]

INFLUENCE OF PHYSICAL LAWS ON CELL GROWTH. Oscar Hertwig investigated the influence of temperature on the recently fertilized ova of rana fusca and rana esculenta, and found that certain well-recognizable stages ("Stadien") in the development of these eggs were reached quicker as the temperature of the breeding medium was increased.[4] He found that the same relation existed between rate of growth and temperature as was known to exist between reaction time and temperature.

Cell volume, within certain limits, is dependent upon osmotic pressure.

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[1] "Schicksale verlagerter u. embolisierter Gewebsteile im thierischen Körper," p. 69, in "Arbeiten a. d. Pathol.-Anat. Abtheilung d. kgl. Hyg. Institut." Posen, 1901, s. 299, O. Lubarsch.

[2] Patholog. Physiologie, second edition, p. 532.

[3] "Nicht von aussen zugeführte Kräfte bringen das Heil, sondern die Zelleschaft es sich selbst."

[4] Archiv. f. mik. Anat. u. Entwicklungsgesch, 1898, 52, 319.

Cells can be made to undergo apparent growth by placing them in solutions the osmotic pressure of which is below the pressure within the cell protoplasm. In this case the cell volume increases by the diffusion of water into the protoplasm. Loeb[1] cut off the polypi from colonies of tubularia, and brought the stems in sea water of various concentrations and dilutions. He found that polypi again grew out of the stumps as long as the sea water was not concentrated to more than 70 per cent. of its volume or not diluted more than to 225 per cent. of its original volume with water; but the regeneration occurred prompter and quicker in the diluted than in the concentrated sea water. Loeb's experiments show conclusively that moderate dilution of the external medium in which a cell is bathed favors growth—*i. e.*, the solution outside must be a hypotonic one. Two other essential physical conditions to growth are (1) a certain turgescence (turgor) within the cell, and (2) expansibility of the enclosing protoplasmic envelope.

It is conceivable that cell protoplasm will become more expansible and looser by the reception of water from the hypotonic environment and a certain turgescence—that is, a hypertonic state within the cell metabolism, and the consequent increase of osmotic energy connected therewith. Increase of turgidity is always seen in rapidly growing parts. Turgidity means osmotic entrance of water into the growing cell. Claude Bernard[2] found that blood flowing through a secreting gland had lost water, and Ranke found that blood that had streamed through a working muscle had lost water.[3] To complete the logic of these instructive observations, Loeb demonstrated that the water thus lost was taken up into the substance of the working muscle; for when the muscle while at rest and before work was placed in a solution which was isotonic with the protoplasmic contents of the muscle cell, it increased in weight during its work[4]—that is, the augmentation of metabolism during work had evidently increased the osmotic pressure within the muscle cell, and the ensuing difference in pressure had induced the growth.

These observations are important for the interpretation of my own studies demonstrating the contraction of fresh cancer cells in solutions made isotonic with the human plasma, or in blood plasma itself, as if they were in a hypertonic solution—a phenomenon not observed when normal cells of the same tissue from which the cancer was taken are placed in the identical plasma or solution. It will hardly be necessary for me to emphasize that any and every growth of and in cancer cells cannot be attributed to the taking in of water only, nor can a muscle hypertrophy due to work be attributed to the taking in of water exclusively. The water osmosis is only one phase of the process of growth, that phase which by effecting an increase of volume impresses us most as growth. The internal construction of the cell household, the deposition of new cytoplasm, is concealed from us.

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[1] Organbildung und Wachstum, Würzburg, 1892.

[2] Phénomènes de la vie, 2d edit., i., 169.

[3] Tetanus Physiologie, 1868, 89.

[4] Pflüger's Archiv., Bd. lxxi., 439.

When frog larvæ are analyzed at different stages of development for their percentage content of water and solid substance it is found that the entire growth of the first fourteen days consists in the incorporation of water. The body weight becomes ten times as great by water, and not until after this does the interior construction and the deposit of solid substances into the aqueous tissue begin. In the first two weeks of development of batrachian larvæ the percentage of water in the embryo rises from 56 per cent. to 96 per cent.,[1] thereafter it begins to sink again. In the light of our present knowledge we have a right to speak of the "osmotic pressure of the cell," for the cell protoplasm, as previously emphasized, is a liquid, a solution, or at least in a state of viscosity. The entrance of water into the cell substance is brought about primarily by metabolic changes effecting a hyperisotonic state in the cell with regard to its surrounding liquid environment. *This phenomenon of change of dimensions (contraction) of fresh carcinoma cells (gastric adenocarcinoma in normal plasma or solutions isotonic with plasma) is to me strong evidence in favor of the view that whatever other causes for the excessive growth of malignant cells there may be, certainly some of the causes are resident within the cell protoplasm itself.*

When we approach a consideration of the question of how the cell builds up protoplasm—that is, an inquiry into the methods and means by which it carries on the synthesis of its substance—we are confronted with a problem apparently presenting insurmountable difficulties, for all artificial syntheses are brought about by forces and agents which can never be conceived as participating in the processes of life. Such agents and forces are high pressure and temperature, concentrated inorganic acids, free chlorine, and galvanic currents of high tension. All of these are factors which would destroy cell life instantly.

So far we know definitely of the synthesis of albumin is only by the aid of enzymes (catalysator). For instance, the reconversion of albumoses, which have been formed in the gastro-intestinal canal into albumin, is attributed to some agent in the gastric wall.[2] When the stomach is isolated from an animal, but kept alive, at the height of digestion all albumoses disappear from it. It might be presumed that this does not indicate a synthesis, but a further breaking down of the albumoses. In that case, however, an increase in the non-precipitable nitrogenous substance should be demonstrable, which is not the case;[3]

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[1] Davenport. "Rôle of Water in Growth," Proceedings of the Boston Society, 28, 73, 1897.

[2] Hofmeister. Zeitschr. f. Physiol. Chemie, 6, 69.

[3] Glässner. Beitr. z. Physiol. u. Pathol. Chemie, 1902, i., 328.

so that any other interpretation of this disappearance of albumoses, except their synthetic reconversion into albumin, appears illogical. Furthermore, Danilewsky and Sawgaloff have proven that chymosin (rennin) is capable of synthetically constructing an albumin from peptones and albumoses in an acid medium. This albuminous body, which they designated as "plastein," is soluble in weak acids and alkalies, insoluble in water, and can be precipitated by strong salt solution—undeniably a typical albumin constructed synthetically by this ferment.

It would be going too far to assume that all syntheses in the organism are enzyme syntheses, for an enzyme (catalyzer) is *incapable of producing anything that would not also be produced without it by other means.* Ostwald[1] groups all ferment or enzyme actions under the term "catalyse," by which he means the *acceleration of a slow or the retardation of a rapid chemical process through the presence of a foreign body (catalysator).*[2]

This definition gives the specific characteristic of enzyme action. An enzyme can, therefore, not carry out a process which would be impossible without it, but it can only influence the time in which a chemical process occurs, generally increasing the rate of the reaction, which would also take place, in a much slower or faster manner as the case may be, however, without it.

The facts, namely (1) that albumin can be constructed synthetically by enzymes, and (2) that enzymes act merely as accelerators or inhibitors of processes that can occur without them, coupled with the experimental results briefly narrated in the preceding (acceleration of cell proliferation by injection of a cell-free and sterile fluid), should suggest the possibility that abnormally rapid formation of protoplasm such as is observed *in the marvellous cell-proliferation of malignant tumors may in some way be associated with the action of an enzyme.* The catalytic origin of malignant neoplasms is by no means proven by these facts and considerations, but only made more probable. I have previously emphasized the important rôle which physical processes (osmosis) play in the growth of cells, so that it is not logical to attribute proliferation to enzyme action alone; but as we have seen that even this osmosis is due in part to a preceding hyperisotonic state within the cell brought about by increased metabolism, the function of a catalyzer is even here not inconceivable, but on the contrary very probable. Much remains to be proven before we are justified in making this conclusion indisputable.

Thus far attempts to isolate enzymes have failed, for what are believed to be ferments are variously considered, albuminous or proteid bodies — albumoses or peptones (Uróblewski) — or nucleoproteids

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[1] Loc. cit.

See W. Ostwald, Ueber Katalyse, Leipzig, 1902.

(Pekelharing's conception of pepsin), in connection with which ferment actions have been observed. In brief, nothing is definitely known of the chemical nature of organic enzymes.

When it comes to the problem of isolating enzymes from protoplasm of cells we find that it presents insurmountable difficulties. It might be thought that inasmuch as enzymes are chemical substances, some of which are known to exert their characteristic action apart from the living substances to which they are usually attached, it might be possible to destroy the cell alone and extract the enzyme; but all protoplasmic poisons are also enzyme poisons (corrosive sublimate, carbon monoxide, sulphuretted hydrogen, hydrocyanic acid, nitrate of silver, formaldehyde, hydrogen peroxide). J. R. Green has emphasized that protoplasm itself has powerful fermentative activity. No matter what the exact relation is that the intracellular enzyme has to the protoplasm, whether it be conceived to be a detached protoplasm molecule or not, as long as it is considered a derivative of protoplasm it must be self-evident that protoplasm is capable of doing all those things which the enzymes can do. Newer conceptions concerning this subject attribute to protoplasm much more wonderful achievements than to the enzymes themselves. If the efforts to separate growth stimulating enzymes from cell protoplasm are at present futile, from the insurmountable chemical difficulties involved, we should realize that protoplasm itself may exert a more intense catalytic action than any enzyme derived from it. Our reflections concerning the nature of a substance which we assume to be capable of stimulating cell growth, and which is cell free and sterile, must end here for the present. We can only say that the agency is contained within the cell, but whether it be a special derivative of the cell protoplasm or the protoplasm itself, it is, in the light of our present knowledge, impossible to decide. A slight hope of advance lies in researches showing differences in the degree of temperature which the protoplasm and the ferment can stand without destruction. I have gained the impression that some ferments are much more susceptible to high temperatures than the protoplasms from which they are derived. For instance, the gastric mucosa of a dog can be heated to a temperature of 158° F. (70° C.) without absolutely destroying the tissue; but heating pepsin to this temperature for three hours will destroy its activity permanently. Similarly, when the so-called "commercial" pepsin is heated to a temperature of 55° to 60° C. in a moist condition it is destroyed (in a thoroughly dry state it may tolerate 160° for a short time). Nevertheless the chemical composition of the nucleo-albumin is still there as it was before the heating. The fermentative power has disappeared. Evidently ferments are not nucleo-albumins in the ordinary sense of the chemist, but something attached and associated with these nucleo-albumins.

CONCERNING THE STRUCTURE OF PROTOPLASM AND ITS CHEMICAL ORGANIZATION. The method that has become most common to familiarize us with the structure of living substance has been to start from histological elements visible under the microscope and to attribute certain physiological functions to them. The conceptions thus derived have not always acquired precision, and we have definite notions only concerning the coarser elements visible under the microscope, such as the nucleus, the chromosomes, etc. This method of observation has not been able to give the least explanation of the finer elements of the cells, the innumerable droplets, barely visible vacuoles and granules of the protoplasm, not to speak of that still finer subdivision of cell protoplasm which might be designated as ultra-microscopic. It is very gratifying, therefore, that biochemists have approached the subject of the construction of the living substance from the purely chemical standpoint, as, for instance, Franz Hofmeister has done (Chemische Organization der Zelle), who did not start from the visible architecture of the cell or protoplasm, but from its achievements and functions. He tried to investigate how protoplasm must be constructed in order to make these functions possible. As the functions of protoplasm are above all things chemical, he entered exclusively upon chemical considerations.

The hepatic cell furnishes us with an instructive example of how many chemical processes may go on in one and the same cell, and very probably go on simultaneously. We know definitely that the liver cell forms glycogen from sugar, and, reversely, sugar from glycogen. It forms urea from ammonia and amido acids. It decomposes hæmoglobin, and under the splitting off of iron it converts it into bilirubin. It can manufacture cholic acid from a substance still unknown, and pairs it with taurin and glycocoll. This same cell can combine phenols with sulphuric acid to form the ethereal sulphates, and it can retain or render harmless poisons that are conducted to it. Nothing is more certain than that these performances represent only a fraction of the chemical versatility of the hepatic cell, for we must certainly assume that the same cell can in addition execute other chemical processes necessary for the oxidation of the food materials brought to it for hydration and assimilation. The supposition that there is a division of labor among the liver cells, one group of cells manufacturing one product and the other another, is untenable because the hepatic cells are of the identical structure throughout the liver, and their relation to the blood, lymph, and biliary vessels so alike that an assumption of a division of labor is not justifiable. There is no escape from the conclusion that all liver cells are chemically equivalent, and each cell is capable of performing all of the described chemical processes and possibly many more. When we reflect that all this chemical activity is invisible by the microscope, and that many chemical processes must occur side by side simultaneously, it is difficult to conceive of the construction of protoplasm that would make such a manifold and wonderful chemical activity possible.

Many years ago Hoppe-Seyler expressed the opinion that such activities in living cells as were intelligible at his period were due to enzymes, and since then it has been possible in many cases to extract such intracellular ferments from the innermost structure of the cells and to establish their significance for vital processes. When we compare the instrumentarium—chemical substances and reagents necessary for chemical transformations in the laboratory—with the processes as they occur in living protoplasm (as much as has thus far been accurately observed) we cannot fail to be impressed with the astounding simplicity and conformity to the end in view exhibited in the means which protoplasm employs to accomplish its chemical purposes. In order to induce a reaction in the laboratory we need a reagent, *i. e.*, either an alkali or an acid, or perhaps the application of heat; but the reagents which the cell employs are calculated to fill the chemist with envy.

The food substances and the oxygen and other possible stuffs which act upon each other within the cell do not, as a rule, belong to the normal cell household, but enter it from the blood. The reagents, however, which induce the reactions, must always be present, and they must in some way be protected from being washed out of their domicile by the constant flow of liquid passing through the cell. These reagents must be either soluble in water or infinitesimally divided in it. They must be capable of accomplishing relatively large chemical performances, and not be consumed or used up during their activity. Such qualities are only known to be possessed by agents which the chemist has designated as *catalyzers*. The bearers of the chemical energy in the cell are catalyzers of a colloidal consistency (Hofmeister). According to Hofmeister, we are justified in assuming that the living cell protoplasm contains all the ferments necessary to the execution of the chemical performances observed in connection with that cell. This view is supported by the knowledge obtained of the physiological chemistry of quite a number of cells in the animal body. For instance, we know that the hepatic cell can yield up (1) a proteolytic ferment, (2) a ferment that can transform combined nitrogen of amido acid into ammonia, (3) a fibrin ferment, (4) a glykase, (5) a maltase, (6) a ferment capable of splitting up nucleins, (7) a lactase, (8) an aldehydase, (9) a lipase, and (10) a ferment similar to the gastric chymosin. Here we have definitely established the presence of ten different ferments in a single hepatic cell. *In addition to this we may believe that the synthetic construction of the cell tissue itself requires a special ferment to make possible the chemical processes necessary for the upbuilding of protoplasm.* From what I have said in connection with normal and abnormal cell growth *it is evident that it is this ferment to which must be ascribed the power of accelerating or inhibiting cell growth.* If we once accept ten different ferments which really have already been definitely established as existing in the same cell, there is no logical reason why the remaining unexplained chemical functions of the cell should not also be ascribed to peculiar ferments, and *I can conceive of no reason why cell growth itself should not be accelerated or inhibited, as the case may be, by a particular enzyme.*

A considerable number of capable modern physiologists have accepted the view that every chemical reaction in the cell has its particular catalyzer corresponding to it. It is easy to recognize that this view may lead us too far, for the specific nature of the ferments is not always such as to restrict their action on one single chemical body, but they may be able to transform a greater or lesser number of substances of similar construction (tyrosinase, for example, may oxidize a large number of aromatic substances). Furthermore, it is conceivable that very labile bodies may arise as a result of chemical transformations in the cells, which are promptly changed into other forms under the existing conditions, and, therefore, no ferment is necessary to explain such transformation. A further revelation which modern chemistry has brought particularly through the researches of Kastle and Loevenhart, to which I have already referred, is the reversibility of the action of ferments. Should this power of reversibility of enzyme action be confirmed with other ferments, it opens up the possibility that many analyses and syntheses are brought about by the same ferment according to the existing requirements and chemical conditions in the cell.

It is probable that the chemical organization of the cell is capable of reckoning with all possibilities, whether they occur within or without the cell, whether they are an advantage or hostile to the cell state. There are no reliable reasons for believing that the organic antitoxins, coagulins, and antihæmolysins owe their origin to definite catalytic cell agents which are equipped for the production of such protective substances. M. Jacoby holds that the antibodies do not act like ferments. The cell is even equipped with ferments for the purpose of committing suicide or digesting itself when it has arrived at a state or condition in which it is no longer of use to the cell state. This phenomenon of cellular autodigestion has recently been observed in tissues which have been perfectly protected from the invasion of microorganisms.

Cellular autodigestion has been studied in all animal organs and occurs in all except those that show a very slight degree of metabolism. M. Jacoby gives to this phenomenon the designation autolysis. It is well known that the various forms of lymphoid cells contain an abundance of a trypsinoid ferment, and it is possible that autodigestion occurs by virtue of such an enzyme. Petrey[1] found that in neoplasms autolysis was much more intense than in normal corresponding tissue. The proteid substances and the nucleins of the cell, the glycogen and the fat, are split up similarly as they would be in the intestines, and a number of diffusible substances result, such as sugar, leucin, tyrosin, fatty acids, etc. This is a form of catalytic colliquidation occurring in single cells, or in cell complexes which have passed the stage of their usefulness; and if this process occurs in an otherwise normal organism there is no reason why the end-products of such cellular autodigestion should not be taken up by the blood and lymph and be absorbed and assimilated to the advantage of the general organism just as they would be if they had been absorbed from the digestive tract.

An astounding fact which has been revealed by modern investigation in connection with this phenomenon is that bactericidal substances are set free during autolysis. It is well known that proteolytic digesting mixtures are first-class culture media for bacteria. For this reason the production of bactericidal substances during cellular autodigestion demands admiration.

If I have in the preceding suggested the probability of the action of intracellular catalytic agents in accelerating or inhibiting cell growth, I do not wish to be understood as meaning that these agents are the only factors which determine the growth and the character of the cell protoplasm. What I have said concerning the rôle of osmosis will prevent my being misunderstood in this connection. An intracellular enzyme cannot construct protoplasm out of itself—it can only build it up out of the materials furnished to it; and as these materials must vary with every species and even with every individual, it is probable that the elements of which protoplasm is constructed within the cell must be presented in a certain definite form, in order that a normal cell protoblast shall result. This is an important point, for it explains how variations in the chemical composition of the cell juices (dyscrasias) may be determining factors for the character of the resulting cell structure.

The simultaneous action of so many intracellular ferments within the same cell sometimes representing diagonally opposite processes, such as oxidation and reduction, hydration and the withdrawal of water, is only conceivable if we accept, with Professor Edmund B. Wilson, the foam structure of protoplasm, that is the view which assumes that protoplasm is held within a foam-like structure of countless ultra-microscopic compartments, retorts, or vacuoles. We must assume also that the walls of these ultra-microscopic spaces are not affected by the reaction which takes place within them. For instance, that the walls of the compartment or vacuole in which oxidation takes place are resistant to the oxidase, and that the walls of the space in which proteolysis takes place are resistant to the proteolytic enzyme. Such a possibility is, so far as our present knowledge goes, only conceivable within the living cell by means of its catalytic agents, which may decompose an albuminoid body of one composition completely and yet leave another very similar albuminoid body entirely intact. For instance, the proteolytic ferment of the liver can completely decompose the globulin of the hepatic substance, but it does not attack another albuminous body of similar composition with which it may even be in contact. The intactness of this so-called foam structure of protoplasm is, therefore, an essential condition for the normal action of the intracellular enzyme. A destruction of these ultra-microscopic partitions may lead to serious consequences, and it is here that the importance of what Welch calls the "more subtle and partial damage of cytoplasm and nucleus" exercises its detrimental influence in destroying the normal intracellular architecture and making possible the liberation of ferments and disturbing the normal chemical equilibrium.

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[1] Hofmeister's Beitr. z. chem. Phys. u. Path., 1902, ii.

We must conceive of the normal and orderly performance of the cell as brought about by the aid of an admirable and highly sensitive system, embracing among other things a transference and transformation of chemical, electrical (ions) and other specific forms of energy, and of accelerating and inhibiting enzymatic (catalytic) agents; of the latter a great variety, each acting in its own ultra-microscopic compartment. We must conceive of a delicate mutual adjustment and conformation to purpose among the many little laboratories within the cell household. And even these conceptions are coarse and inadequate if we knew in reality of the incomprehensible fineness and perfection of intracellular chemical activity. But it will be readily understood that very slight damage to cytoplasm in the sense of Welch[1] will be sufficient to destroy this beautiful arrangement, and enzymes which are useful lambs in the orderly household may become destructive lions when the partitions are broken down.

In the preceding I hope to have made possible the conception that abnormal cell growth may be due to something else than bacteria At the same time I do not wish to deny the possibility of a deleterious influence exerted by bacteria and favoring the development of malignant neoplasms. Malignant neoplasms represent a great group of abnormalities, and I agree with Hansemann that there cannot be a uniform cause for all these manifold types of abnormal cell growth. But if I admit the possibility of bacteria as active in their etiology, it is only as indirect agents in causing these more subtle and partial damages, to cytoplasm, which liberate ferments on the one hand, and destroy them on the other; for we must not lose sight of the possibility that even within the cell abnormal growth may be due to excessive action of one ferment stimulating growth, or to the absence of an enzyme necessary to inhibit it.

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[1] THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, June, 1879, p. 19.

REVERSIBILITY OF ENZYMES. Basing our views on the chemical mechanism of growth on the phenomenon of the reversibility of enzymes, it is intelligible how increase in the dimensions and weight of the cell mass may be brought about by two different and divergent processes. There may be only the synthetic enzyme concerned in the control of growth, or there may be a second intracellular enzyme that inhibits growth, by analysis of protoplasm already formed. Under the conception of enzyme reversibility, however, it is not necessary to assume the existence of two distinct enzymes—one synthetic, the other analytic—for reversibility means that one and the same enzyme may exert diagonally opposite chemical effects if need be. The synthetic enzyme may act like a governor upon the metabolic machine of the cell. If the influx of utilizable substances is normal or subnormal it works synthetically and builds up protoplasm; if the influx is too great it reverses this state of affairs and breaks down protoplasm analytically. We are already very close to the view of the self-regulation of metabolism by reversible enzymes in the case of the liver glycogen, and of fat digestion and absorption. A simpler conception of glycogen metabolism cannot be held than that controlled by an enzyme which converts sugar into glycogen, when there is an excessive ingress of sugar, but reversely converts glycogen into sugar when there is an insufficient influx of sugar.

The metabolism of fat would be readily intelligible if we similarly accept the existence of an enzyme in the fat cells which would be capable by means of its reversibility of maintaining a definite equilibrium between the soaps in the blood and the fats in the fat cells, or which some enzyme (to apply the protothesis to fat digestion) were capable of splitting up fat into fatty acids and soaps within the intestinal lumen, and after their absorption recombining them into neutral fats again.

The doctrine of an intracellular enzyme being active during normal cell growth brings with it the suggestion of a detriment to this enzyme when we are confronted with abnormal cell growth. No doubt the intracellular laboratories are seriously upset, and the anarchistic growth may be due to several possible factors:

1. The self-regulating catalytic mechanism of the synthetic enzyme may be destroyed; it can only build up, no longer decompose.

2. There may have preceded a lesion to the finer structure of the cell substance, a lesion though delicate, yet irreparable, paralyzing the self-regulating catalytic metabolism.

3. The normal tissue tension in the environment of the degenerate

cell can hold it in check for a while if the lesion has struck only one or a few cells—the cell state is threatened by the leaven of rebellion, but perhaps the normal tissue equilibrium of the cell state may be restored if the anarchy has not struck too many cells; they may be forced to autodigestion, or some other form of disintegration, and for all that we know this may occur often if the cell state is vigorous and the metabolism normal.

4. But if the protoplasm apparatus of a considerable complex of cells is disturbed simultaneously, the normal cells in the environment, the tissue juices, etc., are helpless to overcome the excessive growth.

Some have argued that cancers always grow from out of themselves ("aus sicht selbst"—Ribbert); that is, one cancer cell always grows from a preceding cancer cell—until the original degenerate cell is reached. But I can conceive of no reason why the altered metabolism of large groups of malignant cells should not be able to produce such detriment, by chemically affecting adjacent normal cells, that their cytoplasm also receives a subtle damage, sufficient to paralyze the self-regulatory catalytic apparatus for growth (a kind of enzymatic, not bacterial infection). This extension of catalytic infection to other cells, even to the cells of the bloodvessels, is, of course, as yet an assumption; but it is well known that all the various tissues in an autonomous (Lubarsch) neoplasm are in a state of abnormal proliferation, particularly the bloodvessels which give evidence of a peculiar development (Klebs),[1] explainable only on the assumption that this tissue also has been drawn into the cell anarchy, but not to the same extent and character as the cells of the neoplastic parenchyma.

The cell has within its protoplasm certain recognizable structures which may be termed the organs of the cell, viz., the nucleus and its constituents, the chromatophores, centrosomes, the plastids—the passive bodies (E. B. Wilson), the metaplasm or paraplasm, the vacuoles, with their inclusions and secretions, the pigments in certain locations; all of these things signify that the cycloplasmic meshwork is not everywhere in the cell of the same chemical composition or reactive energy. This is already suggested by the fact that widely different reactions, sometimes chemically opposed to each other, occur in the same cell simultaneously. In the cytoplasm, synthetic and analytic transformations occur, not always by the same chemical reactions, but by a series of widely differing reactions. The decomposition of glycocoll to form urea, for example, is not conceivable without a liberation of the NH_2 group from a part of the glycocoll molecule, then follows an oxidation of the remainder, and eventually a combination of the fractional parts. But it is essential that these reactions should occur in well-ordered sequence, otherwise urea cannot be formed in this way. A lawful and ordered sequence of this and numerous similar composite reactions within the cell necessitate the conception that the different agents work separately in different compartments of the cell, we are forced to accept a chemical organization which excludes the idea that the cytoplasm is everywhere the same chemically—*in short, there cannot be an ubiquitous chemical equivalence of protoplasm.* The colloidal reagents then are separated by walls, to them impenetrable and secure from their chemical influence. Let us conceive of a lesion, invisible to the microscope but destroying these partitions, and we can realize the danger of liberation of enzymes; they can now attack all elements formerly inaccessible, or they may even attack each other.

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[1] Pathologie, Bd. xi.

This is the proper place to be reminded of the many theories of the causation of cancer, attributing it to some form of irritation (to which the parasitic theory may be classed also) or to trauma.[1]

METASTASES.—Virchow has expressed the opinion that malignant tumors may extend in three different manners:[2] First, by immediate propagation—that is, by direct extension or growing over from one organ into another; second, by dissemination—that is, detachment of tumor particles which settle down in another position; for instance, if a carcinoma of the stomach extends through or perforates into the peritoneum, the cells of the carcinoma may gravitate to any portion of the peritoneum and cause independent secondary growths. The third manner of extension is highly interesting from the standpoint illuminated in the preceding pages, and in order not to express the views of this great master in a wrong manner I will quote his own words: "This manner of metastatic extension makes it very probable that the transference occurs by means of liquids, and that these possess the power to create an infection ('Ansteckung'), which causes the individual parts to form a reproduction of the same mass which was originally present." Is it not possible that Virchow here conceived of a form of catalytic action? The other two forms of metastatic extension can, of course, not be denied. The third type, however, has been emphatically denied, and has not as yet been recognized by any pathologist of prominence.

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[1] Hemmeter. Cancer Etiology, Diseases of the Intestines, vol. I. p. 677.

It may be objected that I am here moving on very hypothetical ground, and having in the beginning of this article doubted the value of hypotheses, that I am myself now adding assumptions which go beyond the demonstrable state of facts concerning cell growth. But I must contend that I am not formulating a new hypothesis when I assume that all cell growth must be under the control of an intracellular catalyzer; I am simply for the time being using an assumption based on present observations, which, however, have not yet been sufficiently comprehensive. We know of the causal relation between cell growth, cell chemistry, and catalyzers. Certain reactions occur in the cell, certain products are built up, certain substances decomposed. We can isolate the synthetical and analytical products; we have in many instances isolated the enzymes and repeated their characteristic reactions in the test tube. We know from the nature of certain intracellular reactions that they must inevitably occur in separate compartments. Hence we are forced to believe that the growth of the cell structure itself is a separate and distinct performance, that there must be self-regulating cytoplastic syntheses in the cell, and that in pathological cell growth this chemical process is deranged. I am here making temporary use of a "protothesis" (see W. Ostwald, Naturphilosophie, s. 399), with the view that further researches may instruct us whether the assumption is correct or not. The difference between a protothesis and a "hypothesis" is that the former adds nothing to existing observations which cannot further be tested. A protothesis is a temporary conclusion drawn from experience, observation, or experiment, for the purpose of subjecting it to critical testing concerning the limit of its value and significance.

[2] Cellular Pathologie, s. 258.

It was Waldeyer[1] who first demonstrated by systematic investigation that carcinomas grow into the lymph spaces and vessels, and so may reach the general circulation. This observation has been abundantly confirmed; and, furthermore, the characteristic difference has been established that carcinomas readily grow into the lymph vessels, but that the bloodvessels offer them considerable resistance. (It is claimed by Hansemann that sarcomas, on the other hand, may readily break into the bloodvessels.) A number of prominent special investigators of this subject have called attention to the comparative rarity with which metastases occur by the way of the circulation, and Hansemann[2] suggests that a large part of the detached carcinoma cells are destroyed in the blood circulation.

It is essential to distinguish between the local factors which can be recognized as active in the development of a primary tumor and the general factors which determine its future fate, particularly the development of metastases. Of the local factors the most prominent ones have already been sufficiently considered, but the factors which control the formation of metastases are very manifold; and in this connection I should like to call attention to the following: (*a*) Condition of other organs; (*b*) abnormal states of the entire body, the simultaneous action or refusal to act of the regulatory apparatus of the organism; (*c*) acquired or inherited disposition, spoken of as individual disposition (the carcinoma dyscrasia). It is in this connection that the collective investigation of the German government, under the direction of Prof. E. von Leyden, gives promise of throwing light upon the cancer etiology as far as it is associated with bodily constitution, vocation, inheritance, nutrition, manner of living, etc.

In this connection I desire to call attention to a possible explanation of the rarity of metastatic extension of cancers by way of the blood circulation. The idea was suggested by the investigations of Belfante, Carbon, J. B. Bordet, Ehrlich, and Morgenroth, previously referred to. Concerning the hæmolytic action of the serum of one animal upon the erythrocytes of an animal of another species, it is necessary that the effect of the serum of normal individuals upon isolated cancer cells of other individuals should be studied, for it is conceivable that the cancer cells represent forms of protoplasm which have become *so far alienated and emancipated from the general physiological laws of the body that they*

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[1] Virchow's Archiv., 1867, Bd. xli.

[2] Loc. cit., p. 91.

actually represent cells foreign to the body against which the serum brings into action its means of defence just as it would against any other foreign intruder. This is, to my mind, a very hopeful direction for investigation, with a view to prospective prophylaxis or treatment. The point of inquiry will have to be: *"Does not the organism contain in its blood serum defensive substances capable of destroying cancer cells as long as they are not flooding the circulation in excessive quantities? and, if so, how can this natural means of defence be augmented?"* The fact that carcinomas extend preferably by the way of the lymph vessels is highly suggestive of the means of defence in the blood circulation above referred to.

CRITICAL RETROSPECT. In the preceding I have attempted to consider the pathogenesis of cancer from the standpoint of the chemist and physiologist rather than from the bacteriological standpoint. The principal hypotheses were referred to and the difficulties in the way of the acceptance of the parasitic theory briefly given. The changes which cells may undergo under normal and abnormal conditions were presented in the paragraph on "metaplasia." In order to narrow down the point of inquiry the investigations were made upon one type of carcinoma only—that with which the author has greatest familiarity—the adenocarcinoma of the stomach. A *résumé* of recent experiments on tumor transplantation preceded the writer's personal experiments, the main conclusion of which was that gastric ulcers can be experimentally produced, and that the edges of these gastric ulcers can be brought to undergo adenomatous transformation by the injection of a cell-free and sterile fluid obtained from a cancer of the same organ from the same species of animal.

Inasmuch as this filtrate was destroyed after being heated to 60° C., it was concluded that the agent active in causing this abnormal proliferation at the edges of experimental gastric ulcers was a catalytic agent. It might be objected here that the successful experiments were too small in number to permit of reliable conclusions. On this point I wish to state that the experiments extended through years, and at times had to be given up entirely for five to six months for lack of material, because I believed that I could work only with cancer material developed spontaneously in animals, and that cancers even if produced experimentally in the method described did not contain the catalytic agent in sufficient quantity to cause adenomatous proliferation in other animals. The main reason for this is to be sought in the fact that the experimental adenomata are very small; in three out of four cases their recognition depended upon microscopic examination. Although I was and still am in communication with the principal veterinary schools of this country, and even with Professor Ostertag and Professor Regenhogen, of the "Thierärtzliche Hochschule," of Berlin, I have come into the possession of only one dog with cancer of the stomach. The investigations would have been indefinitely delayed had I depended exclusively upon this material. At present I am still engaged with these experiments, and by the aid of Profs. Frank Martin and J. Mason Hundley, whose aseptic technique I hope will secure me a larger number of recoveries from the operations described, I hope to be able to report an additional number of successful experiments in the near future.

The fact that in one instance adenomatous degeneration identical with ulcus carcinomatosum developed at the edges of a pre-existing gastric ulcer spontaneously gives promise of a new source from which to derive canine cancer material. At the same time this spontaneous development of cancer may be interpreted as a criticism of my deductions. It may be argued that the injection of the sterile and cell-free cancer extract does not prove that an enzymatic agent is necessary to start already proliferating cells into a condition of malignancy, for this instance proves that they may pass over into that state without any extraneous agency. Upon closer consideration, however, this criticism can hardly be considered as invalidating the main deductions, for throughout our considerations I have not argued that something entirely extraneous to the cell is needed to cause cancerous proliferation, but; on the contrary, I have tried to emphasize that the agent is something which the cell contains or produces within itself, but its regulatory mechanism is destroyed, etc.

The adherents of the parasitic theory might argue that the cancer extract, though sterile, may contain the products of bacterial metabolism, toxins, etc., which are soluble and can pass through a Pasteur filter, and that it is these toxins which acted as the agency causing the abnormal growth. This objection it is impossible to meet. It might be urged, however, as far as we can judge from the infectious diseases, that bacterial toxins may after injection cause the clinical picture of the disease, but not the characteristic histological alterations in the cells of the tissue which are concomitant with an infection by the living bacteria. Injections of tuberculin, for instance, cannot cause tubercles.

A possible objection is also found in the fact that adenomas of the digestive canal have been caused by mechanical injuries; for instance, by cutting off the lower ends of the glands of Brunner and of Lieberkühn. This observation has not as yet been satisfactorily investigated, and it has not been claimed that adenomas caused in this way were malignant. Lubarsch[1] succeeded in producing a fibro-adenoma in the liver by transplanting a portion of liver into an artificial lesion made in another region of this organ. He does not maintain, however, that this was a malignant—or, as he prefers to designate it, an "autonomous"—neoplasm, and presumes[2] that his experimental neoplasm would have eventually given way to a connective tissue cicatrix.

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[1] Zur Lehre v. d. Geschwülsten, etc., loc. cit., p. 253.

[2] Loc. cit., p. 254.

In the preceding it has been pointed out that the autonomous development of neoplasms (adenomas) may be due to subtle damage to cytoplasm, which is in fact another way of expressing the traumatic and irritation etiology of neoplasms. I do not wish to dispute such possibilities. On the contrary they are to a large extent necessary for the bringing about of deranged catalytic action already described. It is important to emphasize in this connection that I have not succeeded in producing an adenocarcinoma by cutting or bruising the gastric glands, not even when they were in the environment of a pre-existing lesion.

The studies concerning the effect of osmotic pressures upon normal and cancer cells suggest the influence of physical energies upon normal as well as abnormal cell growth, and that future investigations along this line even promise to throw light upon this problem.

The immediate and specific causes of cell division are next considered. The theories of Virchow, Thiersch, Boll, and Weigert are abstracted, and the conclusion reached that the stimulus to normal cell growth is of a chemical nature.

The influence of physical laws upon cell growth constitutes another paragraph, which is followed by a consideration of the question of how the cell builds up protoplasm, that is, the methods and means by which it carries on the synthesis of its own substance. It is here suggested that this is effected by means of intracellular catalyzers.

The conception of how the cell protoplasm must be constructed, its possible chemical organization, concludes with a support of the view accepting the foam structure of protoplasm, and of a special catalyzer regulating the synthetic construction of protoplasm.

As the cell is conceived to be made up of innumerable ultra-microscopic compartments, the more subtle and partial damage of cytoplasm and nucleus in disordering the orderly and normal performances of intracellular catalysis are next set forth.

The reversibility of enzymes is then briefly considered, and the possibility of a damage to the ferment which controls the upbuilding of protoplasm is suggested, and also that there cannot be ubiquitous chemical equivalence of protoplasm.

In the final paragraph on metastases the suggestion is thrown out that possibly the blood serum contains defensive substances effective in the destruction of cancer cells, and the study of this means of defence gives hope of a more successful form of treatment.

In speaking of the transformation which the edges of the experimental ulcer in dogs underwent after injecting the sterile extract of canine gastric adenocarcinoma I may have unwittingly designated them as "gastric adenocarcinomas." What I really mean throughout the article is not that a genuine gastric carcinoma had been produced in my experiments, but that such a histological transformation was effected that the microscopic appearance resembled that of a beginning adenocarcinoma. This expression is as far as the experiments justify me to go. I do not wish to imply that a typical cancer had been produced in this way, for this designation brings with it numerous attributes which it was impossible to bring into the experimental results. Above all things, I am not able to say whether the cell proliferation thus produced experimentally would have gone on to develop a genuine malignant tumor had the animals been permitted to live, or whether the proliferation would have been arrested and its place taken by a cicatrix. To complete the conception of carcinoma we must demand the evidences of malignancy, as is expressed in the production of metastases. Metastases were not produced in any of the animals examined. They occurred only in the dog in which a gastric ulcer had developed spontaneously.

RUBBER TISSUE AS A DRESSING.

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In treating any lesion of the skin in which an ointment is indicated as a dressing, it is of prime importance that the parts should, first, be thoroughly protected from infection from without; second, the ointment used should be kept in constant touch with the parts; third, the dressings, when changed, should come away without sticking and without damaging the new-formed and delicate epithelium, and, fourth, that the dressing should be kept on as long as possible. All these requirements are admirably filled by rubber tissue. The parts having been cleansed with warm sterile water and green soap, should then be dried. The ointment is next spread on and covered over smoothly with sterile rubber tissue. Sterile lint is next applied and the whole secured with gauze bandage. Several cases are cited to illustrate its benefits:

F. J. McA., warrant machinist, U. S. N., aged thirty-three years, native of Brooklyn, N. Y., was, on November 24, 1902, while at work repairing a steam launch, severely scalded by escaping steam on both feet and wrists. The pain was severe, but was relieved by wet picric acid dressings and a hypodermic injection of morphine sulphate, one-quarter grain. The next morning it was found, on removing the dressings, that large blisters had formed. These were punctured, and the serum evacuated with aseptic precautions. A 10 per cent. boric ointment was then applied to the affected parts, and over this rubber